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DEVELOPMENT OF MISOPROSTOL 3-HOUR CONTROLLED RELEASE FORMULATIONS USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

Response surface methodology was used to evaluate in vitro dissolution of misoprostol 3-hour controlled release formulations. Bromocresol green (BCG) as a 1:100 hydroxypropylmethylcellulose (HPMC) dispersion, prepared similarly to misoprostol:HPMC (1:100) dispersion, was employed as a model compound. The variables investigated included concentrations of HPMC, sodium carboxymethylcellulose and lactose. Preliminary experiments indicated that these variables could affect the release kinetics from the formulations, as well as their physical properties (i.e., thickness and hardness). Regression analysis was performed on data generated from the factorially designed experiments. Contour

diagrams of the predicted release profiles indicated that the dissolution profiles were sensitive to the concentration of lactose only in the formulations containing lower (< 4%) concentrations of the polymers. The average percent dissolved and standard deviation at various times were used to select an optimum formulation. The experimental average percent dissolved data for the optimal formula were lower than predicted, but the agreement between BCG and misoprostol was shown to be good. The study indicates the usefulness of the methodology.

INTRODUCTION

Misoprostol is an orally active synthetic PGE_1 analog with mucosal protective and antisecretory properties at daily doses of 800 µg in two (400 µg q12 hr) to four (200 µg q6 hr) divided doses. Misoprostol was difficult to formulate because of its physical state as a viscous liquid and its chemical instability. Subsequently, its stability and ease of formulation were significantly enhanced by its use in an HPMC (1:100) dispersion[1].

Misoprostol is currently available as Cytotec® 200 µg and 100 µg immediate release tablets. Efforts to develop a controlled release dosage form are underway to reduce the dosing frequency thereby improving patient compliance. A misoprostol 400 µg 3-hour controlled release formulation was undergoing a clinical trial at the time this work was initiated. Using the USP Paddle Method at 50 rpm, a typical dissolution profile for a 400 µg controlled

release formulation was 35.7 ± 7.8, 72.0 ± 9.7, 86.0 ± 6.7 and 93.6 ± 4.4 percent dissolved at 20, 60, 120 and 180 minutes, respectively. The objective of the present work was to develop a misoprostol 200 µg 3-hour controlled release formulation that achieved a dissolution profile similar to the misoprostol 400 µg formulation but with less variable dissolution (< ± 6).

To achieve this goal, response surface methodology (RSM) was employed in both the design of experiments as well as the analysis of resulting data. The RSM, first developed by Box et al.[2], has been applied in the development of several sustained and controlled release systems[3,4], but to our knowledge has not been used in the development of a 3-hour controlled release formulation. In this study, factorial experiments were designed to make test formulations from various combinations of the excipients. Each formulation was then tested for disintegration, dissolution, hardness, thickness and weight variation. Response surface regression was used to predict proportions of excipients which would produce the desired dissolution profile.

MATERIAL

Hydroxypropyl methylcellulose (HPMC) 2208 USP 100 cps was obtained from Dow Chemical Company (Midland, Michigan). The sodium carboxymethyl cellulose (NaCMC), USP medium viscosity, was obtained from Aqualon Company (Wilmington, Delaware). Lactose Anhydrous USP and Calcium Sulfate Dihydrate NF were of direct tabletting grade and obtained from Sheffield Products (Norwich,

NY) and Edward Mendell Company (Carmel, New York), respectively. These materials were used without further modifications. The drug misoprostol was synthesized by Searle (Skokie, Illinois). The misoprostol:HPMC (1:100) and Bromocresol Green (BCG):HPMC (1:100) dispersions were prepared by Searle Chemicals (Morpeth, England) and Searle, respectively.

METHODS

The ingredients, except for magnesium stearate, were blended in a suitable V-blender for 10 minutes. The powder blend was then mixed with the magnesium stearate for 2 minutes. The tablets were compressed using a Manesty single punch tablet press (Manesty F-3, Manesty Machines Limited, England) to the targeted hardnesses of 7, 10 and 13 KP and targeted weight of 300 mg. A 11/32" standard concave punch and die set was used. During the response surface study, care was taken to control all fixed variables such as mixing times, press speed and lot numbers of raw materials.

Weight, thickness and hardness of twenty tablets were measured using standard techniques and the averages were reported in milligrams, millimeters and kiloponds (KP), respectively. Tablet disintegration times (DT) weredetermined using the USP disintegration apparatus, with discs and 900 mL water at 37°C. Release of misoprostol or BCG from three to six tablets was determined at selected times (20, 60, 120 and 180 minutes) using the USP apparatus No. 1 (rotating paddle) and 500 mL USP water maintained at 37 ± 1°C, unless specified otherwise. The paddle

speed was held constant at 50 rpm. Samples (2-3 mL) were withdrawn at the various time intervals without replace ment by fresh solvent. The amount of material dissolved was calculated for each sample and corrected for the cumulative amount removed in previous samples.

BCG dissolution samples were assayed at 620 nm using an HP 8451A UV/VIS spectrophotometer. Misoprostol dissolution samples were analyzed by HPLC, using a variable wavelength detector set at 200 nm and a C-8 column (15 cm X 4.6 mm i.d). The mobile phase consisted of acetonitrile:water (50:50). A flow rate of 1.5 mL/min was maintained and the injection volume was 200 µl. The average percent dissolved at each sampling time was reported, unless specified otherwise.

RELEASE PROFILE ANALYSIS

The release of the drug from a planar surface of an insoluble, heterogeneous matrix by diffusion through the intergranular openings created by the porosity of the matrix was described by the Higuchi square-root equation[5]:

$$Q = \sqrt{D\varepsilon\frac{C_s}{\tau}t(2A - \varepsilon C_s)} \qquad (1)$$

where Q is the cumulative amount of drug released per unit area at time t, D is the diffusion coefficient of the drug in the dissolution medium, ε is the porosity of the matrix, C_s is the

solubility of the drug in the dissolution medium, τ is the tortuosity of the matrix, and A is the concentration of the drug in the tablet, expressed as g/mL. The equation predicts a straight line relationship if Q is plotted versus $\sqrt{t}$.

EXPERIMENTAL DESIGN

Stage I: In order to find optimal concentrations of excipients, a 2^3 factorial design was used to generate design points. Lactose concentration ranged from 0 to 30%. These values were based on prior formulation experience with the drug. Total polymer concentration ranged from 2.5 to 15.0%. This constraint on the total polymer concentration limited the usually cubic design space to the trapezoidal solid shown in Figure 1. The centroid point was included to test the curvilinear effect. In addition, the centroid point was made in duplicate to test lot-to-lot variability. The design points were:

Formulation	NaCMC (%)	HPMC (%)	Lactose (%)
5	2.5	0.0	0
8	15.0	0.0	0
10	2.5	0.0	30
4	15.0	0.0	30
7	0.0	2.5	0
2	0.0	15.0	0
1	0.0	2.5	30
9	0.0	15.0	30
3	4.375	4.375	15
6	4.375	4.375	15

The drug and magnesium stearate concentrations were kept constant. The concentration of calcium sulfate, however, was adjusted to

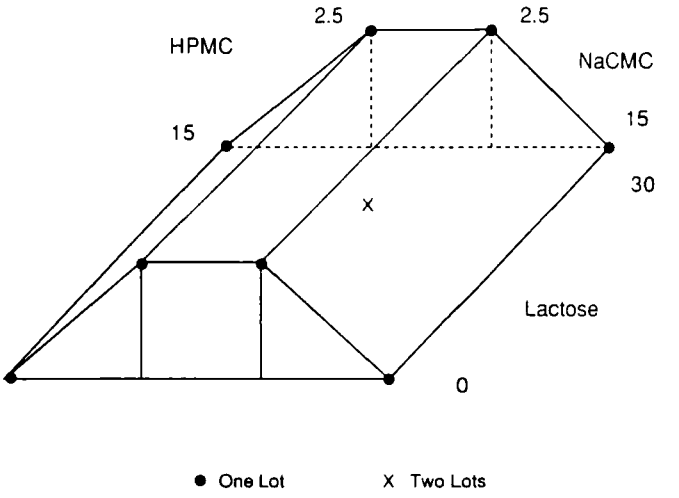

FIGURE 1
Schematic diagram of Stage I experimental design with 2^3 constrained factorial.

keep the tablet weight constant (300 mg). These formulations were made in randomized order.

Stage II: Based on the results of the analysis of the Stage I dissolution data, a further experiment was designed to better define the acceptable concentrations of excipients. In addition, a choice was made to use only NaCMC as the polymer. A 2^2 factorial experiment with a center point was designed as follows:

Formulation	NaCMC (%)	Lactose (%)
12	0.5	30
11	0.5	0
10	2.5	30
5	2.5	0
13	1.5	15

Two of these lots had been made in the first experiment. The remaining lots were made in randomized order.

STATISTICAL ANALYSIS

Response surfaces were fit to each of the four dissolution time points and each of their respective standard deviations for a total of eight models for Stage I using SAS®. The regression models included main effect and interaction terms as well as separate intercepts for each hardness level as follows:

$$\text{Response} = \alpha_{\text{hardness}} + \beta_1(\text{NaCMC}) + \beta_2(\text{Lactose}) + \beta_3(\text{HPMC}) + \beta_{12}(\text{NaCMC*Lactose}) + \beta_{13}(\text{NaCMC*HPMC}) + \beta_{23}(\text{Lactose*HPMC}) \quad (2)$$

Often response surface models include squared terms [e.g., β_{33} (HPMC*HPMC)]. There were not sufficient degrees of freedom, however, to estimate these terms individually. As a result, these terms are confounded (mathematically inseparable) with the interaction terms. For Stage II, the regression surface modeling was repeated without the HPMC terms (in equation 2) using the five formulations listed.

RESULTS AND DISCUSSION

Preliminary Release Profile Analysis

To gain insight into the mechanism of matrix behavior, cumulative drug release was plotted against the square-root of time. The best fitting line correlation coefficients from such plots are listed in Table 1. It is interesting to note from Table 1 that in general the tablets which remained intact (DT > 15

TABLE 1

Summary of the Linear Regression Analysis on Q vs. √t Plot and Disintegration Time

Form.	Intercept	Slope	r	DT (min)
1	51.73	13.03	0.888	10.28
2	-47.21	11.08	0.996	>30
3	-26.02	11.24	0.993	>30
4	-37.58	9.70	0.992	>30
5	-20.04	13.14	0.996	15.21
6	-40.20	9.94	0.997	>30
7	-28.76	14.98	0.998	>30
8	-25.74	6.62	0.996	>30
9	-45.96	12.32	0.989	>30
10	-35.46	15.76	0.999	9.36
13	-35.46	15.76	0.999	9.57

minutes) in the disintegration test deviated least from linearity ($r > 0.990$). These findings are consistent with those of Touitou and Donbrow[6]. They reported that the hydroxyethyl methyl cellulose (HEMC) matrices which remained intact in the disintegration test gave drug release related to the square-root of time (i.e., matrix diffusional model). Lapidus and Lordi[7], on the other hand, found that the Higuchi model for diffusional release from inert matrices was applicable to whole tablets only during a relatively short initial stage, after which the tablets disintegrated or underwent attrition which caused deviation from initial pattern.

Contrary to the findings of Lapidus and Lordi, 11 out of 13 formulations in this study exhibited square-root of time relationship. The physical condition of the tablet matrix during

TABLE 2

Comparison between Paddle and Basket Methods

Time (min)	Percent Dissolved: Formulation 3 @ 7 KP Paddle[a]	Formulation 3 @ 7 KP Basket[a]	Formulation 3 @ 10 KP Paddle[a]	Formulation 3 @ 10 KP Basket[a]	Formulation 14 @ 10 KP Paddle[a]	Formulation 14 @ 10 KP Basket[b]
20	14.02±2.43	6.74±3.34	14.02±2.43	3.01±0.65	21.84± 3.78	55.78±2.53
60	31.13±4.88	17.95±1.04	26.92±2.47	16.48±1.13	44.72± 5.91	103.50±2.82
120	35.94±6.30	30.92±1.32	49.89±6.50	29.01±1.29	69.58± 9.41	108.86±1.79
180	68.89±7.29	52.56±7.26	62.71±6.63	47.94±1.74	84.19±10.49	113.13±1.09
Linear Regression from Q vs. $\sqrt{t}$ Plot:						
Slope	11.03	9.87	11.24	9.71	14.14	12.09
Inter.	-25.90	-36.20	-26.03	-40.58	-19.20	80.05
r	0.934	0.975	0.993	0.987	0.999	0.882

[a]50 rpm stirring speed.

[b]100 rpm stirring speed.

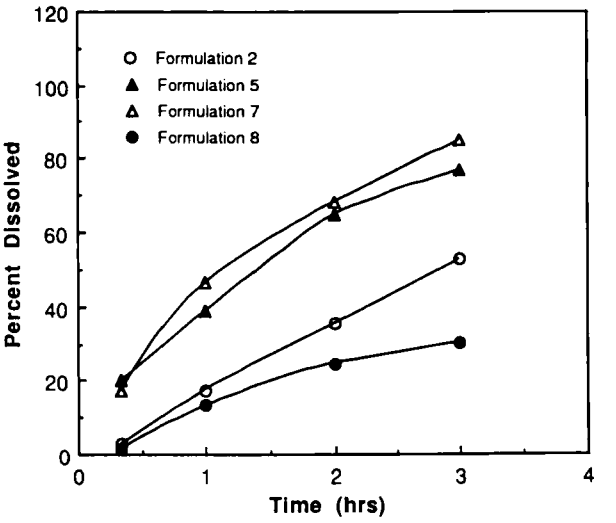

FIGURE 2
Release profiles for BCG from formulations without lactose compressed at the hardness of 10 KP.

the course of the dissolution run may be a possible explanation for the observed linearity ($r > 0.990$). For example, while using the paddle method, it was found that the hydrated polymer held the tablet matrix together during the course of dissolution runs (3 hours). Also, when a higher polymer content was used, the bottom of hydrated tablet matrix was tightly bound to the dissolution vessel creating a "pseudo-planar" release situation. Higuchi's Q vs. $\sqrt{t}$ relationship was derived for a planar release system and could very well be applicable to the "pseudo-planar" system in this study. Such a situation, however, did not prevail while using the basket method and correspondingly the observed linearities were not good ($r < 0.990$ for Q vs. $\sqrt{t}$ plot, see Table 2).

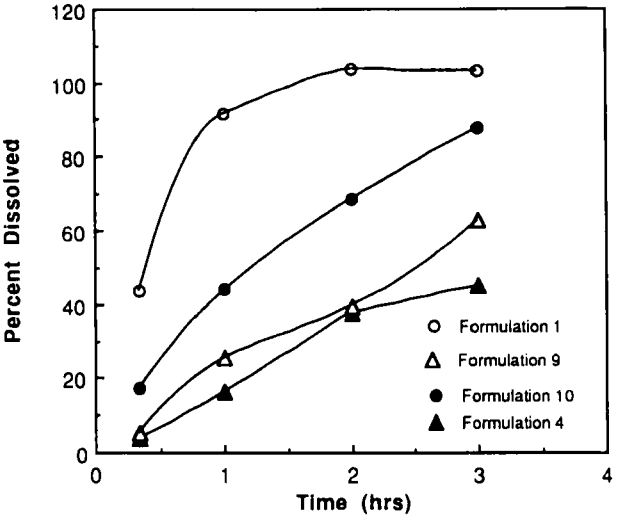

FIGURE 3
Release profiles for BCG from formulations with 30% lactose compressed at the hardness of 10 KP.

BCG release profiles from various formulations compressed at a hardness of 10 KP are shown in Figures 2 and 3. These formulations contained 0 or 30% lactose. In general, the formulations containing HPMC released BCG faster than the formulations with NaCMC, as expected based on the difference in the viscosity grades of the two polymers (100 cps vs. 700 cps). For the formulations containing 30% lactose and 2.5% polymer, HPMC released ~100% BCG in 1 hour compared to NaCMC which released ~80% BCG in 3 hours (Figure 3). For the other formulations containing these two polymers, however, the differences in the BCG released at various times were not so large. It should be noted that despite the difference in excipient concentrations, both formulations 7 and 10 gave close to the desired dissolution profile.

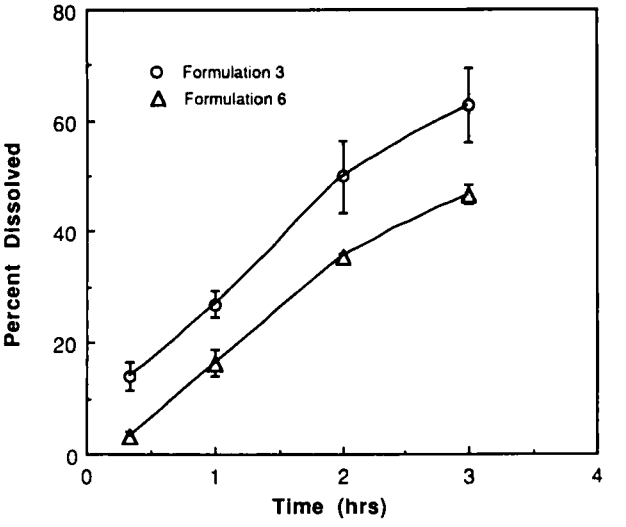

FIGURE 4
Release profiles for BCG from formulations 3 and 6 compressed at the hardness of 10 KP.

The release data for the formulation containing the mid-levels of lactose (15%) and polymers (8.75%) are summarized in Figure 4. As mentioned in the experimental design section, this centroid point was repeated (formulations 3 and 6), but poor reproducibility was observed. The likely sources are the variability in the dissolution testing procedure and/or the variability in the formulation physical parameters. Examination of the formulation physical parameters (e.g., weight, hardness, friability) showed that the weight variation (RSD < 0.6%), the hardness values (RSD < 5%) and the friability values (< 0.5% for 10 and 13 KP tablets) were acceptable. Examination of the dissolution method, however, revealed that the paddle method resulted in more variability in the dissolution profiles than the basket method (Table 2). It can be seen from Table 2 that except

for a one data point, the variability using the paddle method was greater than that using the basket method.

Response Surface Analysis

As stated in the experimental section, a constrained factorial design (Stage I) was used to investigate the effects of the three formulation variables on the dissolution properties of the tablets. In general, the model fits to the average percent dissolved surfaces were good ($r^2 > 0.9$) and indicated significant sensitivity due to the concentrations of excipients. The model fits to the standard deviation surfaces were also good ($r^2 > 0.8$) but indicated no significant sensitivity, implying that variability is relatively unaffected by excipient concentrations. Lactose speeded the dissolution while NaCMC and HPMC slowed the dissolution. Both NaCMC and HPMC, however, had highly correlated parameter estimates, indicating comparable slowing effects on the dissolution rate.

The use of contour diagrams allows visual understanding of the significance of the regression equations by demonstrating the contribution of the variables, as well as their interactions and curvature effects, to the measured response. Figure 5 shows the contour diagrams of the mean percent BCG released as a function of lactose and NaCMC concentrations but without HPMC at a hardness of 10 KP. Figure 5 illustrates that at lower levels of NaCMC (< 5%), lactose had significant effect on the release profiles. At higher levels of NaCMC (> 10%), however, the release profiles were independent of the lactose levels as shown by the nearly vertical lines.

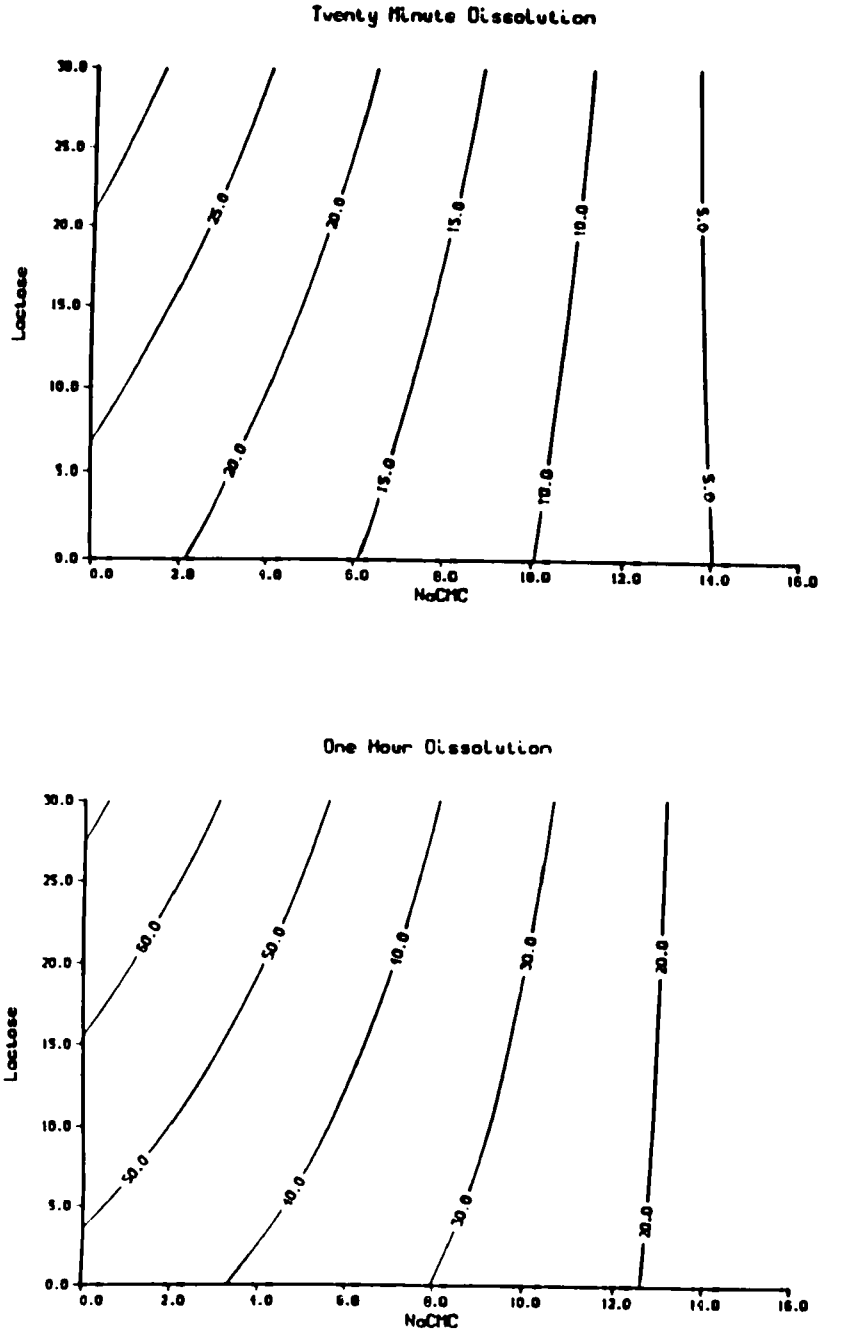

FIGURE 5
Contour diagrams for the calculated percent dissolved as a function of the lactose and NaCMC concentrations at 20, 60, 120 and 180 minutes.

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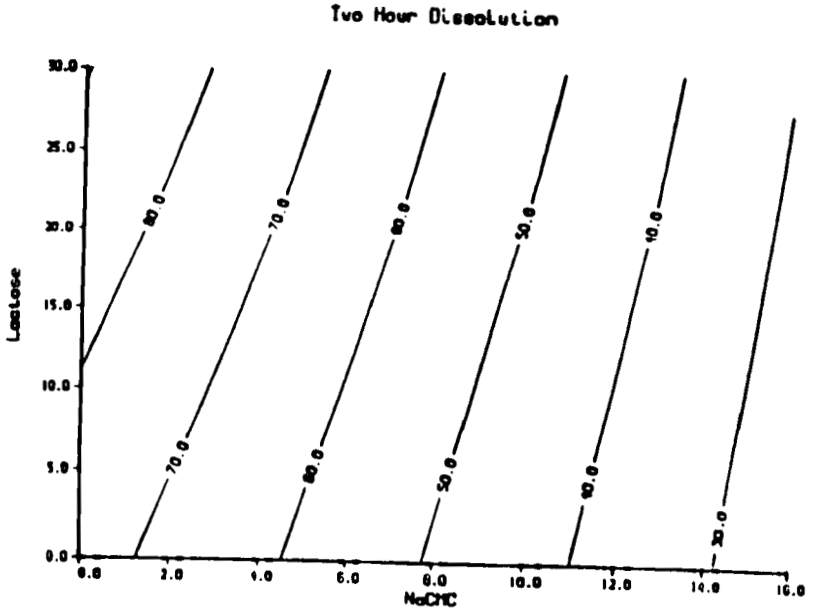

Figure 5 Continued

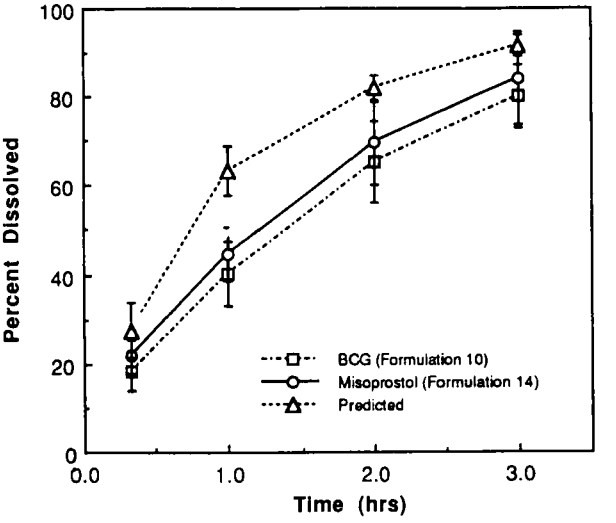

FIGURE 6
Comparison of experimental and predicted release profiles from a formulation with 2.5% NaCMC and 30% lactose.

Contour plots from the four dissolution models combined with a grid search were used to predict the levels of lactose, NaCMC and HPMC which would give the desired dissolution profile. Several formulations showed acceptable dissolution profiles based on this analysis - the analysis predicted 27.61 ± 6.12, 63.35 ± 5.53, 82.02 ± 2.82 and 91.66 ± 2.50 percent release at 20, 60, 120 and 180 minutes, respectively, for formulation 10. One lot of misoprostol formulation (formulation 14) with the same composition as BCG formulation 10 (2.5% NaCMC, 30% Lactose, 0% HPMC) was prepared for comparison. The dissolution profile for the misoprostol lot was slightly faster than that of the BCG lot, but well within the variability of the assay. Both were, however, slower than the predicted profiles from the model (Figure 6). A

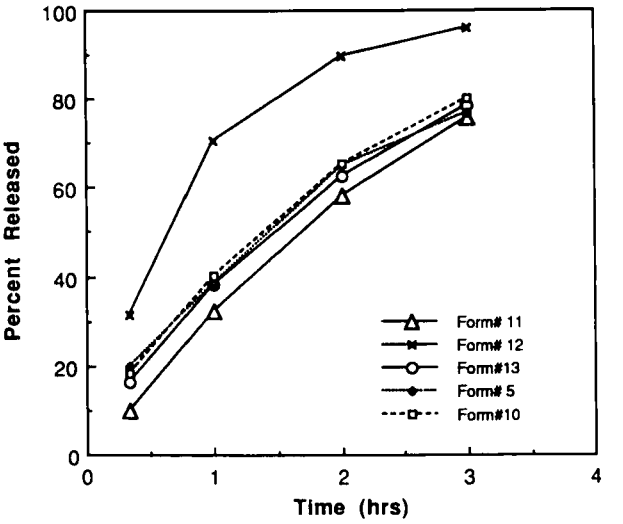

FIGURE 7
Release profiles for BCG from Stage II formulations compressed at the hardness of 10 KP.

good correlation between misoprostol and BCG release data justified continued use of BCG:HPMC dispersion in place of misoprostol:HPMC dispersion, which in turn permitted a quick quantitative assessment of dissolution data and conserved analytical time in addition to several other resources.

Based on the Stage I model fits, a factorial design (Stage II) was used to investigate the effect of low levels of NaCMC with 0 to 30% lactose levels. HPMC was dropped from the study due to a Forest patent[8], limiting its use in controlled release dosage forms. Release profiles for the Stage II formulations are shown in Figure 7. It can be seen from Figure 7 that in the formulations without lactose (5 and 11), decreasing the NaCMC level decreased the release rate which is the opposite of what was expected. It should be noted that the calcium sulfate levels were

increased when the lactose levels were decreased to keep the tablet weight to 300 mg. The calcium sulfate being both water-insoluble and water-immobile may have decreased the release and may have contributed to the observed effect. Formulation 12 (0.5% NaCMC and 30% lactose) showed very close to the optimum release profile but the standard deviations around the average percent released were unacceptably high (e.g., 70.69 ± 18.00 at 1 hr). This analysis suggested that the optimal formulation has ~2.5% NaCMC and 30% lactose. Further decreasing the NaCMC increased the variability and decreasing the lactose decreased the average percent released at 2 and 3 hours.

CONCLUSIONS

The release of BCG from formulations was affected by two different polymers (HPMC and NaCMC), their concentrations and the concentration of lactose in the system. In general, formulations containing HPMC released BCG faster than formulations with NaCMC and both decreased the release with increasing concentrations. In contrast, formulations containing low levels of NaCMC and lactose decreased the release with decreasing concentration of NaCMC. Increasing concentrations of both water-insoluble and water-immobile calcium sulfate may have contributed to this decreased BCG release. Release from eleven of the thirteen formulations exhibited the square-root of time relationship. The physical condition of the tablet matrix during the course of the dissolution run may be a possible explanation for the observed linearity

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